Survival in multiple myeloma patients who develop second malignancies: a population-based cohort study

Survival in multiple myeloma (MM) has improved significantly during recent decades both in younger and older patients.[1,2] The improved survival is considered to be primarily due to new treatment options in MM, including high-dose melphalan with autologous stem cell transplantation,[3] the immunomodulatory drugs and proteasome inhibitors.[4,5] Recently, second malignancies have gained great clinical and scientific attention in MM as three randomized clinical trials reported an increase in second malignancies associated with lenalidomide maintenance treatment.[6] In a newly published meta-analysis, exposure to lenalidomide plus oral melphalan was found to significantly increase hematologic second malignancies.[7] Previously we showed that MM patients had a 26% increased risk of developing any second malignancy when compared to the general population, and an 11-fold increased risk of developing acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS).[8] In the United States, second or higher-order malignancies are the third most common cancer diagnoses.[9] With improved survival in MM patients, second malignancies are expected to increase in the near future and possibly contribute to problems of disease management. Importantly, it has been shown that the cumulative risk of death from MM outweighs the risk of death due to second malignancies.[6] For the individual patient who develops a second malignancy, however, the outcome is of great importance. We conducted a large population-based cohort study, including all patients diagnosed with MM in Sweden, over a period of more than 50 years. This study aimed to investigate the effects of second malignancies on survival and assess changes following the introduction of modern myeloma therapy. Furthermore, as AML/MDS is over-represented in MM patients, we assessed patterns of survival specifically in these patients.

All patients diagnosed with MM from January 1 1958 to December 31 2011 were identified from the Swedish Cancer Register. Information was collected on sex, date of birth, and date of MM diagnosis. All subsequent second malignancy diagnoses were identified through cross-linkage within the Swedish Cancer Registry, and the type and date of the second malignancy documented. For each MM patient with a second malignancy, 1-3 patients without a second malignancy from the MM cohort were randomly selected and matched by age (+/- 3 years), sex, and date of MM diagnosis (+/- 1 year). The matching criteria also required that all the patients without a second malignancy had to be alive when the corresponding matched MM patients developed a second malignancy. Patients with non-identifiable match (5%) and those diagnosed with MM or a second malignancy at autopsy were excluded. Survival was estimated from the date of the second malignancy diagnosis and the same date for matched MM patients without second malignancy until death, emigration, or end of study (December 31 2012), whichever occurred first.

To analyze AML/MDS more thoroughly, we identified all patients with AML/MDS from the group of MM patients with a hematologic second malignancy. Each patient with MM and AML/MDS was matched by age (+/- 3 years), sex and year of AML/MDS diagnosis with 4 patients having *de novo* AML/MDS, and 4 patients diag-

Table 1. Risk of death in multiple myeloma patients with a second malignancy compared to patients without a second malignancy.

	HR	95%CI	*P*	1 year* (%)	5 year** (%)
Overall MM with a second malignancy (1547)	2.3	2.1-2.5	<0.001	52 *vs.* 81	18 *vs.* 30
Hematologic (n=200)	4.9	3.8-6.4	<0.001	27 *vs.* 82	9 *vs.* 33
Gastrointestinal (n=364)	3.4	2.8-4.1	<0.001	39 *vs.* 82	13 *vs.* 30
Male reproductive (n=220)	1.3	1.1-1.6	0.011	70 *vs.* 79	24 *vs.* 26
Female reproductive (n=60)	2.2	1.4-3.4	<0.001	57 *vs.* 87	29 *vs.* 39
Breast (n=95)	1.3	0.9-1.8	0.176	78 *vs.* 84	31 *vs.* 37
Kidney and urinary tract (n=112)	1.9	1.4-2.6	<0.001	55 *vs.* 77	12 *vs.* 30
Non-melanoma skin cancer (n=229)	1.4	1.2-1.8	<0.001	70 *vs.* 79	20 *vs.* 28
Melanoma (n=62)	1.3	0.9-1.9	0.236	81 *vs.* 83	23 *vs.* 36
Respiratory (n=68)	5.2	3.2-8.2	<0.001	25 *vs.* 81	8 *vs.* 32
Oral, nasal and pharyngeal (n=20)	2.9	1.4-6.3	0.006	55 *vs.* 85	15 *vs.* 34
Endocrine (n=25)	1.1	0.6-2.0	0.792	68 *vs.* 82	47 *vs.* 28
Nervous system (n=35)	5.1	2.7-9.8	<0.001	37 *vs.* 85	19 *vs.* 33
Bone and cartilage (n=5)	0.7	0.2-2.6	0.558	80 *vs.* 69	40 *vs.* 8
Soft tissue and mediastinal (n=15)	5.8	2.1-16.4	<0.001	53 *vs.* 89	8 *vs.* 34
Unspecified tumors (n=37)	14.2	6.0-33.9	<0.001	14 *vs.* 79	0 *vs.* 23

*MM: multiple myeloma; HR: hazard ratio; CI: confidence interval; n: number of MM patients diagnosed with each second malignancy type. Risk of death in multiple myeloma patients with a second malignancy (n=1547) compared to matched multiple myeloma patients without a second malignancy (n=4019). Survival was estimated from second malignancy diagnosis and the same date for matched MM patients without a second malignancy diagnosis. Patients with each second malignancy type are compared to matched MM patients without a second malignancy. Cox proportional hazard model for matched data was used to calculate hazard ratios (HRs) and 95% confidence intervals (CI). Kaplan-Meier method was used to estimate 1- and 5- year survival. Two-sided P<0.05 was considered statistically significant. *One-year survival is reported for second malignancy type* versus *matched MM patients without a second malignancy. **Five-year survival is reported for second malignancy type* versus *matched MM patients without a second malignancy.*

nosed with AML/MDS as a second malignancy (referred to as "secondary AML/MDS"), excluding patients with non-melanoma skin cancer and MM as the primary cancer diagnosis. Analyses were performed for each second malignancy type. In addition, survival in MM patients with AML/MDS (n=95) was compared to matched MM patients without a second malignancy. A separate analysis was performed for patients with MM and AML/MDS compared to matched patients with *de novo* AML/MDS (n=380) and to matched patients with secondary AML/MDS (n=380). To assess survival patterns before and after the introduction of modern myeloma therapy in Sweden, survival analyses were conducted for two different time periods, 1958-2000 and 2001-2011, including MM patients with and without a second malignancy in both calendar periods.

A total of 26,627 patients were diagnosed with MM in Sweden during the study period. Of these, 1547 (5.8%) patients developed a second malignancy and were matched to 4019 MM patients without a second malignancy. Median age at MM diagnosis was 70 years (74 years at second malignancy diagnosis). Median time to second malignancy diagnosis was 2.7 years.

Overall, MM patients with a second malignancy had a statistically significant 2.3-fold (95%CI: 2.1-2.5; P<0.001) increased risk of death in comparison to MM patients without a second malignancy (Table 1 and Figure 1A). Median survival was 1.1 years (95%CI: 1.0-1.2) after second malignancy diagnosis and 3.0 years (2.8-3.1) after corresponding date for MM patients without a second malignancy (P<0.001).

Multiple myeloma patients with AML/MDS had a 8.5-fold (5.5-13.2; P<0.001) increased risk of death compared to matched MM patients without a second malignancy. The median overall survival was 2.4 months (1.7-3.6) in MM patients with AML/MDS and one-year survival was 16%.

Patients with MM and AML/MDS had a statistically significant 1.7-fold (1.2-2.1; P<0.001) increased risk of death compared to matched patients with *de novo* AML/MDS. Patients with MM and AML/MDS did not have a statistically significant increased risk of death (1.2; 0.9-1.5; P=0.180) compared to matched patients with secondary AML/MDS (Figure 1B).

Risk of death for MM patients with and without second malignancy according to different time periods is presented in Table 2 and Figure 1C, and show that MM patients with second malignancies in 2001-2011 had a statistically significant 1.3-fold (1.1-1.5; P=0.005) increased risk of death compared to MM patients without second malignancies in the period 1958-2000.

Overall, we found that second malignancies negatively impact survival in MM patients. The inferior survival in MM patients with second malignancies is most likely multifactorial. One could argue that previous treatment with chemo- and radiotherapy leaves patients in a frail condition which could be the main culprit,[10] or that inherent factors specific to MM or the second malignancy are responsible. Furthermore, patients already treated for MM who develop a second malignancy might only be able to receive sub-optimal treatment due to toxicity problems. Taken together, the impact of second malignancies on survival is significant and clinically relevant for the individual patient, and warrants attention and further research.

Our findings, that survival in both MM patients with and without a second malignancy has been improving from 1958-2000 to 2001-2011, are extremely interesting. Possible explanations are that, overall, survival of patients with second malignancies has improved,[11] or it could be that new treatment options in MM are less toxic, thus leaving patients in a better condition to receive later treatment. Although survival in MM patients with a second malignancy has been improving, MM patients diagnosed with a second malignancy in 2001-2011 had a 30% higher risk of dying compared to

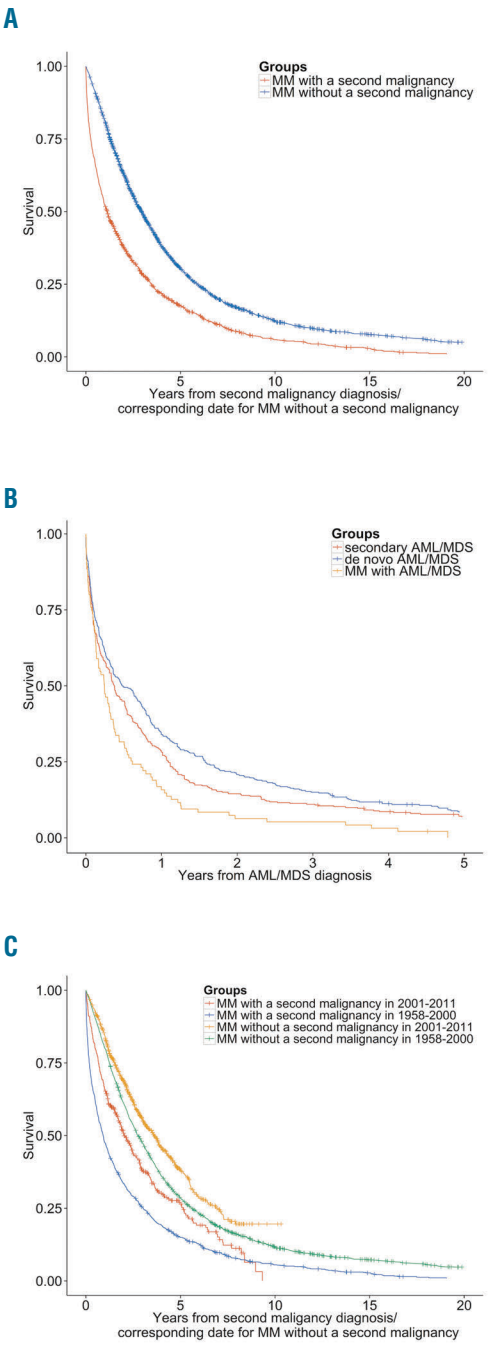

Figure 1. (A) **Kaplan-Meier curve of survival in multiple myeloma (MM) patients with and without a second malignancy.** (B) Kaplan-Meier curve of survival in patients with MM and acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS), patients with secondary AML/MDS and patients with *de novo* AML/MDS. (C) Kaplan-Meier curve of survival in MM patients with and without a second malignancy, before and after the introduction of modern myeloma therapy.

Table 2. Comparison of risk of death in multiple myeloma patients with and without a second malignancy according to different time periods.

	HR	95%CI	P
MM without second malignancy 1958-2000 (n=2968) *versus* MM without second malignancy 2001-2011 (n=1051).	1.3	1.1-1.5	<0.001
MM with second malignancy 1958-2000 (n=1164) *versus* MM with second malignancy 2001-2011 (n=383).	1.5	1.3-1.8	<0.001
MM with second malignancy 2001-2011 (n=383) *versus* MM without second malignancy 1958-2000 (n=2968).	1.3	1.1-1.5	0.005

MM: multiple myeloma; HR: hazard ratio; CI: confidence interval; n: number of patients are compared in each analysis. Cox proportional hazard model was used to calculate HR and 95%CI, adjusting for age, sex and year of MM diagnosis.

patients without a second malignancy diagnosed before the introduction of modern myeloma therapy (1958-2000). This is an important observation given the expected increase in the number of patients with a second malignancy due to improving survival rates.[1,2]

Multiple myeloma patients who developed AML/MDS had a median survival of only 2.4 months and a 16% one-year survival. These are worse outcomes than reported in a recent case series where a median overall survival of six months was observed.[12] In an analysis comparing survival between MM patients with AML/MDS and patients with *de novo* AML/MDS, we found that they had a 70% higher risk of dying. However, a comparison of MM patients with AML/MDS to patients with secondary AML/MDS showed no difference in mortality. To our knowledge, this is the first time that such a comparison has been made in MM patients. Previous studies have reported that patients with therapy-related/secondary AML/MDS in general have a worse prognosis than patients with *de novo* AML/MDS,[13] with the cytogenetic profile thought to be one of the most important prognostic factors for survival.[14] Engelhardt *et al*. recently reported that 8 patients with MM and AML/MDS had complex chromosomal aberrations at AML/MDS diagnosis.[15] Further research is needed to build upon these findings.

Our study has several strengths, including a large sample size, long study period, and application of high quality population-based data from Sweden. By using the nationwide register-based design, where data are gathered prospectively, we were able to account for recall bias and ensure the generalizability of our results.

Limitations include the lack of detailed clinical and treatment data, as well as information on the molecular subtype of MM and the second malignancy. In the analyses where MM patients with and without second malignancies are compared between calendar periods, the selection of MM patients without second malignancies was not matched; however, in these analyses we adjusted for age, sex, and date of the MM diagnosis.

Taken together, in this large population-based cohort study including almost 27,000 MM patients diagnosed during five decades, we confirmed and expanded on prior findings regarding survival in patients with MM and second malignancies. We showed that a second malignancy is associated with a poor outcome and made important new observations regarding survival patterns after the introduction of modern myeloma therapy. Furthermore, we showed that the diagnosis of AML/MDS in MM patients is dismal, yielding a worse outcome than matched patients with *de novo* AML/MDS. These results emphasize the importance of identifying risk factors for second malignancies in MM patients.

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